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# The KRN mouse model of inflammatory arthritis

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**Abstract.** In 1996 a new murine model of spontaneous arthritis was described by the group of Benoist and Mathis. Mice transgenic for a T cell receptor recognizing an epitope of bovine RNase and bred onto a NOD background developed severe destructive arthritis, which resembles human rheumatoid arthritis in many respects. The development of disease requires the presence of T and B lymphocytes and is dependent on the MHC class II molecule I-$A^{g7}$. B cell activation by antigen and an additional CD40-CD40 ligand interaction was found to give rise to the production of autoantibodies. Glucose-6-phosphate isomerase was identified as the target of the autoantibodies; moreover, the transgenic T cells were demonstrated to exhibit a dual specificity for both bovine RNase and glucose-6-phosphate isomerase. Importantly, the arthritis is serum transferable to normal recipients, enabling the examination of the pathogenic mechanisms of joint inflammation and destruction. Recent studies suggest the crucial involvement of the innate immune system in the development of antibody-induced arthritis. Complement components, Fc receptors and neutrophils are indispensable for disease induction. An overview of the existing data is given and the emerging concepts of the pathogenesis of the K/BxN arthritis are discussed with respect to their relevance for human rheumatoid arthritis. Because of the reliable and robust induction of joint inflammation by serum transfer this new disease model has been and will be a valuable means to address the as-yet-unanswered key questions related to the development of arthritis.

## The KRN transgenic mouse line, a fortuitously discovered new arthritis model

In a paper in Cell in 1996 the group of Diane Mathis and Christoph Benoist first described a new spontaneous mouse model of rheumatoid arthritis (RA), the KRN transgenic mouse line [22]. It is a good example of how serendipity is often involved in major scientific advances. The researchers intended to study positive selection of T cells recognizing a peptide of the bovine pancreas ribonuclease in the context of I-$A^k$ [35]. To this end they generated a transgenic mouse line carrying the rearranged

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**Table 1.** Similarities and differences to human rheumatoid arthritis

| | K/BxN | Rheumatoid arthritis |
|---|---|---|
| Arthritis | Symmetrical<br>Chronic progressive | Symmetrical<br>Chronic progressive |
| Joints involved | Hip joints spared | DIP joints spared |
| Spine involvement | Yes | No |
| Rheumatoid factor | No | Yes |
| Joint destruction | Yes | Yes |

T cell receptor (TCR) genes from the T cell hybridoma R28. Whereas the resulting offspring expressed the transgenic TCR in the thymus as well as in the periphery, the T cell compartments of animals on the selecting H-$2^k$ and nonselecting H-$2^b$ backgrounds were very similar, indicating a lack of a significant positive selection. So the KRN mouse line proved unsuitable to answer the questions initally asked by the researchers, but Kouskoff et al., "quite fortuitously" as they state, crossed the KRN mice to the NOD strain [22]. Surprisingly, transgene-positive KRNxNOD F1 mice displayed severe joint inflammation of all distal joints. The disease showed a complete penetrance with a disease onset around the age of 4–5 weeks. The clinical picture with symmetrical, severe, deforming polyarthritis was much reminiscent of RA (Table 1). The KRN mouse line was therefore proposed as a new model for the human disease rheumatoid arthritis [22]. In this article the pathogenesis of the arthritis in the KRN mouse line, further designated with the newer nomenclature K/BxN, is discussed. Similarities to and differences from RA will be highlighted and the significance of this new disease model for arthritis research will be addressed.

## The pathogenesis of arthritis in the K/BxN mouse model

### The role of T cells

In the KRN TCR transgenic mice spontaneous arthritis development was only seen in transgene positive F1 offspring of KRN-C57BL/6xNOD (K/BxN) crosses, but not in crosses between KRN-C57BL/6 (KRN-B6) and other inbred strains [22]. The important role of the NOD MHC genes was indicated by experiments using a B6 line congenic for the NOD MHC crossed to KRN transgenic mice, which resulted in arthritic offspring. Further studies pinpointed the MHC class II molecule I-$A^{g7}$ as the decisive element derived from the NOD background responsible for arthritis development. BALB/c mice carrying an $A_\beta{}^{g7}$ transgene crossed to B6 mice carrying the TCR transgene resulted in offspring that developed arthritis indistinguishably from K/BxN mice. The crucial dependence of arthritis development on I-$A^{g7}$ indicated that I-$A^{g7}$-restricted T cells are involved in the pathogenesis of arthritis [21, 22, 28].

The analysis of the T cell compartment provided evidence for clonal deletion of the R28 TCR transgenic T cells in young K/BxN mice (neonates until 3 weeks of age). However, at 3 weeks of age mature single-positive cells appeared in the thymus and subsequently also in the periphery, albeit at reduced numbers. It was speculated that potentially autoreactive receptors escaped clonal deletion because of incomplete allelic exclusion leading to rearrangement and expression of endogenous TCR-$\alpha$ and

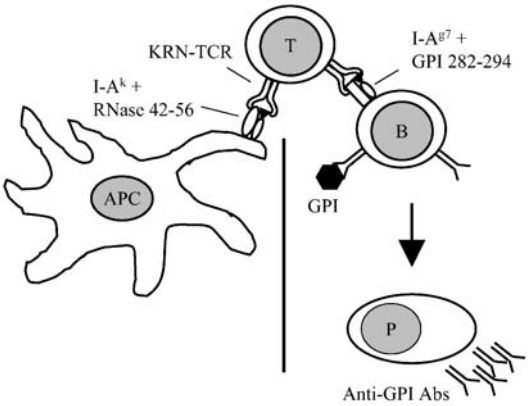


**Fig. 1.** Dual specificity of the KRN TCR responsible for an autoimmune response. The KRN T cells (*T*) bear a transgenic TCR which has a dual specificity for the bovine RNase peptide 42–56 in the context of I-A$^{k}$ (shown in the *left half* of the figure), as well as for the peptide GPI 282–294 in the context of I-A$^{g7}$ (*right half*) [2]. In K/BxN mice B cells (B) displaying I-A$^{g7}$ can function as antigen-presenting cells (*APC*) and present the autoantigen peptide GPI 282–294 to specific T cells and in turn receive help to differentiate into plasma cells (P) producing the arthritogenic anti-GPI autoantibodies (*GPI* glucose-6-phosphate isomerase)

-β genes resulting in relatively reduced levels of transgene expression. The TCR transgene-bearing T cells are functionally impaired with weak responses against p41–61 of bovine RNase. Nevertheless, their expression of surface markers was slightly increased, demonstrating activation in vivo. Kouskoff et al. [22] even succeeded in examining synovial T cells, which showed an enrichment of CD4$^{+}$ T cells, and among the CD4$^{+}$ population an enrichment for high levels of transgene expression. Due to the low cell numbers, no functional studies could be undertaken. Further proof of the T cell dependence of the arthritis was demonstrated by injecting the K/BxN mice with a non-depleting anti-CD4 antibody. When administered at the latest 5 days before arthritis onset, disease could be blocked completely. Antibody injection at later time points did not change the course of the arthritis. This latter finding indicated that the arthritis development was dependent on TCR transgene-positive T cells early in the pathogenesis but not at later stages when clinically apparent disease had already developed.

Concerning the T cell specificity, it was initially found that the R28 TCR showed alloreactivity to NOD antigen-presenting cells [22]. This was proposed as the basis of arthritis development. However, later it became clear that T cells in the K/BxN mice were actually autoreactive against glucose-6-phosphate isomerase (GPI) in the context of the self-MHC molecule I-A$^{g7}$ [2, 29] (Fig. 1). GPI is a ubiquitous enzyme of the glycolytic pathway and will be discussed in the context of the autoantibody production in K/BxN mice.

## The role of B cells

The role of B cells in the pathogenesis of arthritis in the K/BxN mice was initially assessed by introducing the μMT° mutation, which resulted in an absence of mature

B cells in the K/BxN mice. K/BxN mice devoid of B cells did not develop arthritis [22]. Further evidence for the mechanism by which B cells are involved in the pathogenesis of arthritis came from arthritis transfer experiments. Lymphocyte-deficient C57BL/6-RAG (B-RAG) mice were injected with splenocytes from K/BxN donors. The recipient mice developed arthritis, however K/BxN splenocytes depleted of either T or B cells were unable to induce arthritis upon transfer into B-RAG mice. Transfer experiments also demonstrated that arthritis is dependent on I-$A^{g7}$ expression on B cells. This clearly indicated that B cells were directly involved in the pathogenesis of arthritis via an I-$A^{g7}$-restricted recognition mechanism [21]. The fact that CD40 deficient K/BxN mice were protected from arthritis suggested that B cells were activated, presumably by $CD4^+$ T cells via a CD40L-CD40 interaction [21]. To find out whether a specific B cell product could initiate arthritis, serum from K/BxN mice was transferred into various hosts. Arthritis developed in B cell-deficient as well as normal C57BL/6 hosts, with histological features resembling the spontaneously occurring disease in K/BxN mice. The main difference was that the serum transfer-induced arthritis was only transient. Joint inflammation starts to subside between 15 and 30 days after serum transfer. Histological analysis 35 days after the serum transfer revealed almost complete disappearance of inflammatory infiltrates and intact cartilage with signs of regeneration. However, arthritis could be maintained by repeated injection of serum. The IgG fraction of the serum was shown to be responsible for the arthritis induction, indicating the existence of arthritogenic IgG in K/BxN serum [21].

## Specificity of arthritogenic immunogobulins

In 1999 Matsumoto et al. [29] described the identification of the arthritogenic IgGs. The glycolytic enzyme GPI was found to be the target of both the disease-inducing T cells as well as the pathogenic IgGs. Analysis of the repertoire of arthritogenic IgGs in the K/BxN model revealed high frequencies of GPI-specific B cell clones in the spleen and other lymphoid organs. For induction of arthritis anti-GPI monoclonal antibodies (mAbs) needed to be injected as pools of at least two different mAbs, which recognized different epitopes [27]. Furthermore, arthritis development was dependent on the presence of mAbs of the IgG1 isotype in the pools. The requirement of more than one mAb for disease induction was previously reported for the induction of collagen-induced arthritis (CIA), where mAbs of the IgG2 isotype were more efficient in inducing arthritis [43]. In general, the more individual mAbs injected the more efficient was the disease induction. This suggested that the formation of large immune complexes enhanced the pathogenicity.

## The role of innate immune mechanisms

With the identification of GPI as the autoantigen for CD4 T cells and B cells, a picture emerged in which a break of tolerance leads to the activation of the adaptive immunity resulting in the production of an arthritogenic autoantibody. How this autoantibody production translates into inflammatory and destructive events in the joints is still unclear. A detailed analysis of the genetic influences on the end-stage effector phase of the arthritis in K/BxN mice revealed a prominent role of the C5 locus, coding for the comple-

ment component C5, of the chromosome 2 [14]. The subsequent evaluation of the complement system revealed that C5-deficient animals did not develop antibody-induced arthritis, and treatment of wild-type mice with anti-C5 mAb could even reverse ongoing disease [15]. Further analysis of the complement pathways demonstrated that the activation of the classical pathway was not needed for arthritis induction, since C4-deficient mice developed arthritis to the same extent as wild-type recipients [15, 42]. In contrast, in the absence of factor B, a member of the alternative pathway, most of the animals did not develop arthritis and in the ones that did it was very weak [15]. How the alternative pathway is activated is still unknown and will be discussed below.

There is a dual requirement for the alternative complement pathway as well as for the presence of FcγR. The finding that injection of serum of arthritic K/BxN mice into FcRγ-deficient mice did not induce arthritis suggests that the pathogenic action of anti-GPI mAbs depends on FcγR activation [7, 15, 23]. The high-affinity FcγRI as well as the low-affinity FcγRIII employ the common γ-chain FcγR. Whereas a FcγRI null mutation was without influence on the arthritis, in the absence of FcγRIII the inflammatory response was attenuated compared to wild-type mice, but not completely abolished, indicating the involvement of another receptor depending on the common γ-chain [7, 15]. Interestingly, FcγRIIIA gene polymorphisms have previously been associated with susceptibility to RA [34].

FcγR is expressed on mast cells, neutrophils, macrophages and NK cells. Upon FcγR engagement these cells are activated and secrete tumor necrosis factor (TNF-α) and interleukin-1 (IL-1), as well as chemokines [38]. FcγR activation (predominantly through FcγRIII) by GPI-anti-GPI immune complexes could, therefore, lead to the production of inflammatory cytokines and degradative enzymes by macrophages, neutrophils and mast cells, resulting in arthritis in the K/BxN mice. In this model, mast cell activation and degranulation may heavily contribute to neutrophil recruitment and the acute phase of paw swelling, and macrophages may play a role later in the pathogenesis of disease [7, 8, 25]. Thus, the results indicate a prominent role of the pathways of the innate immune system in the pathogenesis of arthritis in the K/BxN model.

## Inflammation and joint destruction in K/BxN mice

Although the pathogenesis of RA is still unknown, it is well established that the inflammatory cytokines TNF-α and IL-1 play an important role in the development of RA. Clinical studies using anti-TNF-α mAbs, soluble TNF-α-receptor (TNFR) as well as anti-IL-1β mAbs have clearly shown a beneficial effect in a majority of RA patients [6, 26, 45]. Early studies in K/BxN mice revealed an increased production of IL-6 and TNF-α in arthritic joints [22]. Given the importance of TNF-α in RA, the effect of TNF-α blockers were determined in K/BxN mice. Injection of anti-TNF-α mAbs did not alter the course of arthritis in K/BxN mice [16, 23]. However, the relatively mild arthritis following K/BxN serum transfer showed a reduced incidence in TNF-α-deficient recipient mice [16]. This finding suggested a role for TNF-α, although not an absolute requirement, in the arthritis development. Interestingly, environmental rather than genetic influences governed the susceptibility of the TNF-α-deficient recipients to arthritis upon serum transfer. The fact that arthritis in animals deficient for TNFR was similar to controls [16, 23] suggests the involvement of other TNF-α-dependent signaling pathways, using so far non-identified TNFR.

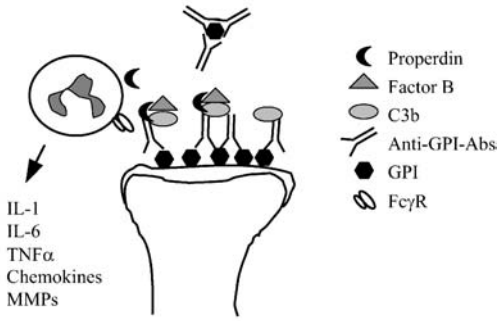


**Fig. 2.** Activation of the innate immune system by arthritogenic anti-GPI antibodies. GPI is deposited on the cartilage surface in the joints and anti-GPI autoantibodies bind to the deposits, forming immune complexes. Because of a relative lack of complement regulatory proteins on cartilage surface, complexes with C3b can form. Properdin produced by neutrophils immigrating into the joint then enables binding of factor B resulting in activation of the alternative pathway of complement. Inflammatory cells recruited into the joint are activated by the immune complexes via their FcγR to produce inflammatory cytokines, chemokines and degradative enzymes (a neutrophil is shown representatively) (*MMP* matrix metalloproteinases)

In contrast to the situation in TNFR-deficient mice, IL-1R gene-targeted mice did not display any signs of arthritis after serum transfer [5, 16]. This result is similar to other murine arthritis models [37, 44, 49], establishing a crucial role for this cytokine in arthritis. The dominant role of IL-1 might be explained by the fact that IL-1 seems to function in series with TNF-α. TNF-α can induce IL-1 production by synoviocytes and IL-1 blockade is able to inhibit arthritis in TNFα transgenic mice [3, 37]. However, in RA patients IL-1 antagonists are slightly less effective than TNF-α inhibitors [11]. In the K/BxN serum transfer model, the administration of Toll-like receptor-4 (TLR-4) agonist was able to circumvent the requirement for signaling through the IL-1R [5], suggesting that targeting IL-1 may be insufficient to prevent signaling through the common pathway that the TLRs and the IL-1R share.

Macrophages are considered the primary source of proinflammatory cytokines in the joints. However, neutrophils, which are abundant in inflamed joints, are also able to secrete TNF-α and IL-1 in addition to degradative enzymes. Administration of neutrophil-depleting antibodies to recipient mice before or concurrent with K/BxN serum transfer resulted in a complete inhibition of disease [46]. Surprisingly, even established joint inflammation could be reversed with neutrophil-depleting antibodies administered as late as 3 days after serum transfer [46]. Thus, neutrophils seem essential for the induction of joint inflammation in the K/BxN serum transfer model. The chemotactic effects of C5a-C5a receptor ligation attracts neutrophils to sites of inflammation [12]. These in turn produce properdin, which binds C3b-IgG complexes, leading to association with factor B, resulting in activation of the alternative pathway of complement [15, 41] (Fig. 2).

Subsequent inflammatory mechanisms are felt to result in focal bone erosions, which are a hallmark feature of RA. In both the KRN serum transfer model and human RA there is a dissociation between visually detectable joint swelling and the progression of bone erosions [7, 26, 31, 33, 36]. Strong evidence indicates that osteoclasts are involved in the erosive process. Analysis of the subchondral sites of erosions in RA patients revealed acid phosphatase-positive multinucleated cells [4], and in situ hybridization studies showed mRNA expression of tartrate resistant acid

phosphatase and cathepsin K at sites of bone erosions, which are typical markers for osteoclasts [9, 13]. Osteoclast differentiation is under the control of TNF-related activation-induced cytokine (TRANCE), also known as receptor activator of NF-κB ligand (RANKL), osteoprotegerin ligand or osteoclast differentiation factor [1, 24, 48, 50]. Hence, osteoclasts are absent in TRANCE/RANKL- deficient mice, which display severe osteopetrosis [20]. Transfer of K/BxN serum into TRANCE/RANKL-deficient mice resulted in paw swelling, which was clinically similar to control mice. However, in contrast to the inflammation, bone erosions were dramatically reduced as assessed by micro-CT and histopathological analyses [36]. These results support previous findings in adjuvant arthritis in mice treated with osteoprotegerin [19]. In the light of the critical role of osteoclasts in focal bone erosion, targeting osteoclast differentiation by inhibition of TRANCE/RANKL signaling may represent a promising therapeutic strategy in RA.

## Mechanisms responsible for joint specificity

Since the autoantigen GPI is present in all tissues, normally in the cytoplasm but also in soluble form in human serum, the question of the joint specificity arises. Several mechanisms could hypothetically explain the joint specificity of the anti-GPI response. One simple explanation would be overexpression of GPI in the joints. However, reverse transcription-PCR analysis of GPI mRNA from joints revealed no differences in GPI transcript levels in joint versus kidney. The sequences of the GPI transcripts in the joints did not differ from the reference sequence in the GenBank, which ruled out that particular GPI isoforms could be responsible for the joint specificity [29, 30]. Moreover, two-dimensional polyacrylamide gel electrophoresis did not reveal evidence for translational and post-translational modifications of GPI in the joints. GPI was expressed homogeneously in all cells including chondrocytes and synoviocytes, as assessed by immunohistochemistry [30]. In addition, GPI was detectable extracellularly on the cartilage surface in K/BxN mice and to a lesser extent in normal mice. Double staining with antibodies against IgG confirmed the presence of immune complexes in arthritic K/BxN but not in normal mice [30]. Interestingly, immune complexes were detected also in extra-articular tissues of K/BxN mice, but, in contrast to the joints, the complement component C3 did not colocalize, suggesting that extra-articular immune complexes do not fix complement [22, 30]. These immune complexes form locally in the joint, but also circulate in the serum. Injection of preformed GPI immune complexes into naïve mice, however, did not confer arthritis, in contrast to injection of anti-GPI antibodies [30]. Consistent with this finding, visualization of injected anti-GPI antibodies showed accumulation in the joints within minutes, arguing against the need for a prior immune complex formation in the serum [47].

Based upon these results, Matsumoto et al. [30] put forward the hypothesis that GPI, forming deposits on the cartilage surface in the joints, possibly binding to cartilage proteoglycans via multiple low affinity interactions, leads to the local formation of immune complexes [30]. The cartilage surface differs from other tissue surfaces in its relative lack of complement-regulatory proteins, such as the cell membrane-bound C3 inactivator decay-accelerating factor and membrane cofactor of proteolysis. This could explain the increased susceptibility to the activation of the alternative complement pathway. Taken together the existing evidence indicates that the proper-

ties of the joint cartilage rather than the antigen is responsible for the joint-specific autoimmune manifestations. The findings in the K/BxN mice also demonstrate that, surprisingly, in this autoimmune arthritis the adaptive immune system activates innate immune mechanisms rather than the other way round, which is usually seen during an immune response against invading microorganisms.

## Relevance for human RA

In spite of great research efforts, the etiology and pathogenesis of RA remain largely in the dark. When rheumatoid factor (RF) was discovered, RA was believed to be caused by autoantibodies. However, RF was found in chronic infections, neoplasms and even in normal individuals. Additionally, the transfer of serum of patients with active RA did not induce disease in the recipients, which argued against a causative role of RF in the pathogenesis of RA [10]. Later it emerged that the expression of the HLA alleles DRB1*0401, DRB1*0404 and DRB1*0101 are associated with severity of RA [32]. Since MHC class II molecules govern positive and negative selection of CD4 T cells in the thymus, a decisive role for these cells as pathogenic effectors was postulated. However, up to the present day no autoantigen with a causal relationship to RA could be identified. Based upon animal models of arthritis type II collagen, heat shock protein 60, human chondrocyte gp39 and others have been proposed as autoantigens. However, only a minority of RA patients have detectable autoantibodies against these putative autoantigens. The new arthritis model by Benoist and Mathis now adds GPI to the list of potential autoantigens. Several groups have examined the presence of anti-GPI antibodies in patients with RA and other forms of arthritis. Schaller et al. [39] reported increased anti-GPI titers in 64% of 69 RA patients but not in patients with Lyme arthritis or Sjögren's syndrome in serum. Cloning of anti-GPI IgGs from RA patients revealed somatic mutations and high replacement to silence ratios, which indicates an antigen-driven affinity maturation of the autoantibodies. Moreover, they detected significantly increased GPI concentrations in RA serum and synovial fluid as compared to Sjögren's sera and osteoarthritis synovial fluids [39]. These findings contrast those of other groups. Schubert et al. [40] reported only 2 of 61 sera of RA patients as positive for anti-GPI antibodies using recombinant human GPI [40] and similarly, Kassahn et al. [17] studied anti-GPI antibodies in 462 sera of patients with various rheumatic diseases, and detected reactivity to GPI in only a few cases of RA as well as in other diseases. Subsequent reevaluation of their data by Schaller et al. revealed that a large proportion of the patient population they had studied suffered from Felty's syndrome, which may explain the higher percentage of anti-GPI-positive sera they found. In view of these conflicting results, the role of anti-GPI autoantibodies in the pathogenesis of RA is not clear and needs further investigation. Should a clinically identifiable subgroup of RA patients have high titers of anti-GPI antibodies this would argue for an important pathogenetic role of GPI as an autoantigen in RA and implicate new therapeutic options. Anti-GPI Fab fragments administered either systemically or locally into affected joints could be used to block the binding of pathogenic anti-GPI antibodies to GPI deposited in the joint, and thereby prevent FcγR-binding and complement activation.

Moreover, the fact that autoantibodies recognizing ubiquitous antigens cause joint-specific disease revived the interest in B cells as important effector cells in RA, as has been assumed in earlier years following the discovery of RF. Based on the da-

ta with the K/BxN mouse model, B cell-directed therapies could be beneficial in RA. In addition to B cell-depleting therapies, strategies aimed at inhibiting B cell activation seem very promising. Studies in K/BxN mice have shown that blockade of the CD40-CD40L interaction can prevent arthritis development [23]. Transplantation experiments in primates indicate that blockade of B cell costimulation induces a long-term effect without a need for continuous administration of the blocking drug [18]. Treatment of established arthritis would, however, require additional administration of an anti-inflammatory agent, at least initially, as long as preformed arthritogenic antibodies are present in the joint. Candidates include agents interfering with the components of the innate immune system providing the link between the activated adaptive immune system and downsteam events of the joint disease, complement components and FcγRIII. In spite of the unclear relevance of the K/BxN model of arthritis for RA, it will certainly prove useful in the future to test new therapeutic approaches based on the results of studies on the basic pathogenetic mechanisms involved in the arthritis induction.

## Conclusions

The new arthritis model K/BxN displays many similarities to human RA (Table 1). The arthritis occurs spontaneously with a penetrance of 100% and is strictly associated with a particular MHC class II allele, the I-$A^{g7}$ derived from the NOD background. Arthritis development is dependent on $CD4^+$ T cells and B cells, both specific for GPI, a ubiquitous enzyme of the glucose metabolism. CD4 T cell-dependent B cell activation by GPI, together with a costimulatory signal via CD40L-CD40 interaction leads to the production of arthritogenic anti-GPI autoantibodies. How antibodies against GPI can induce arthritis is incompletely understood. The available data, however, indicate a crucial involvement of the innate immune system. Arthritis does not develop in FcγR knockout mice, nor in mice deficient for components of the alternative pathway of complement. Similarly, neutrophil- and mast cell-deficient mice show minimal signs of joint inflammation after transfer of arthritogenic antibodies. GPI is deposited on the surface of the joint cartilage, which serves as a ‘molecular sink’ for various proteins. Elegant studies showed binding of anti-GPI antibodies to GPI on the cartilage surface in vivo, forming local immune complexes. In contrast to other organs, e.g. kidney, there is complement activation on the cartilage surface, probably due to a lack of complement regulatory proteins. Activation of the alternative pathway of complement then leads to a local inflammatory reaction. Thus, the joint specificity of the autoantibodies is determined by the properties of the target tissue rather than by the expression or distribution of the autoantigen. Whether the situation in the K/BxN mouse model resembles the pathogenic events in RA is unclear. Anti-GPI antibodies have been detected in a proportion of RA patients but also in other forms of arthritides. It is controversial whether there is a predominance in RA, but some evidence suggests that there are significant anti-GPI titers in patients with Felty’s syndrome.

Although the relevance of this model for RA is not known, it is of great value for arthritis research. First, the transfer of arthritogenic antibodies into mutant mice allows the investigation of the downstream events of the pathogenesis of RA: the inflammatory and destructive local processes in the joint. In this respect this model is also a valuable tool to test new therapeutic applications, especially since it can be as-

sumed that these terminal effector functions are similar in the various forms of arthritis. Other advantages of the anti-GPI antibody-transfer-induced arthritis are the rapid onset of arthritis within a week after the transfer and the relative strain independence. The latter allows the use of various knockout and transgenic animal strains as recipients, without the need for backcrossing. Of greater importance is the question of how tolerance to the ubiquitous self-antigen GPI is lost. This break of tolerance and the subsequent activation of innate immune mechanisms represent crucial events not only for the development of arthritis, but also for many other organ-specific autoimmune diseases. The careful dissection of the early events in the development of the spontaneous arthritis in the K/BxN mice might therefore advance our understanding of basic mechanisms of autoimmunity, and hopefully provide new insight into the still mysterious pathogenesis of RA.

**Note added in proof:** Matsumoto et al reported a low prevalence of anti-GPI antibodies in patients with rheumatoid arthritis, thus GPI does not appear to be an autoantigen common to the majority of patients with rheumatoid arthritis (Arthritis Rheum 48: 944).

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